REMARKS

Amendments to the Claims

Claim 1 is amended to recite components consisting of substantially pure gonococcal antigens. Support is throughout the specification, for example, at page 6, lines 29-31, page 8, lines 6-8, and page 15, lines 1-5. Claim 1 is amended to recite that the composition is an immunogenic composition. Support is at page 7, lines 30-31. Claim 1 is amended to recite the protein names. Support is at page 1, lines 25-31, page 3, lines 15-17, and page 4, lines 26-29. The claim 1 amendment to recite 70% or more identity is supported in the claims as filed.

New claims 18-24 recite a composition comprising both an OmpA protein and a PPIase protein with varying identity to SEQ ID NOS 2 and 4, respectively. Support is at page 2, lines 10-20, and page 3, lines 15-20.

Objection to the Specification

The specification is objected to for containing un-capitalized trademark recitations. Applicants have amended the specification to capitalize trademark recitations and, where relevant, recite generic equivalents. Please withdraw the objection.

Rejection Under 35 U.S.C. § 112 ¶ 1

Claims 1, 2, and 4 stand rejected under 35 U.S.C. § 112 ¶ 1 as lacking written description. The Patent Office contends that Applicants do not adequately describe the genus of sequences having 70% or more identity to SEQ ID NO:2 and SEQ ID NO:4, where the sequences "retain prophylactic functions against homologous and/or

heterologous *Neisseria gonorrhea* in humans or non-humans." Office Action at pages 5-6. Applicants respectfully traverse the rejection.

Claims 1 recites an immunogenic composition; *i.e.*, a composition that raises an immune response, not a prophylactic composition as the Office Action contends. The immunogenic composition comprises two or more components where each component consists of a gonococcal antigens having 70% homology to the recited sequences. SEQ ID NOS:2 (OmpA) and 4 (PPIase) are currently under examination.

What is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter. *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005). Here, these factors support a conclusion that the specification adequately describes the claimed genera of antigens.

The effect of a mutation on a protein's function depends strongly on the function of the protein. This correlation is recognized in the Written Description Training Materials (Rev. 1, March 25, 2008):

> [T]hose of skill in the art might require more or less correlating information depending on the kind of protein activity. If activity X is simply structural, e.g., a member of the collagen class, correlating information might not be a critical factor. However, if activity X is enzymatic, and there is no disclosure of the active site amino acids residues responsible for the catalytic activity, lack of that kind of correlating information may be a problem.

Training Materials at page 39. Here, the issue is whether a protein sequence having at least 70% identity to each of SEQ ID NOS:2 and 4 is immunogenic. Unlike catalytic

activity, where the function of the entire enzyme can be lost by a single amino acid change, an immune response requires the presence of only a single immunogenic peptide along the entire length of the protein. For the recited genus of proteins to lack the ability to stimulate an immune response, the amino acid changes would need to both (i) destroy *every* immunogenic region along the length of the protein and (ii) not *create* any new immunogenic regions within the protein.

Computer analysis of Applicants' SEQ ID NO:2 (OmpA) show that the likelihood any protein encompassed within the scope of the claims will contain no immunogenic region at all is vanishingly small. SEQ ID NO:2 encodes a 225 amino acid OmpA protein. Applicants enclose Exhibit 1, a Kolaskar[1] analysis of immunogenicity, which shows the numerous antigenic regions in the protein encoded by SEQ ID NO:2. Peaks indicating predicted antigenic peptides are distributed across the entire length of the protein. In fact, a Kolaskar analysis underestimates the number of antigenic regions in a protein: comparing their computer-based analysis to actual immunogenicity data, Kolaskar showed that an analysis of 34 different proteins identified only 122 antigenic determinants out of 169 experimentally known antigenic determinants. Page 173, col. 2 ¶ 1. Thus, the protein encoded by SEQ ID NO:2 likely contains even more antigenic determinants than the computer analysis in Exhibit 1 suggests.

Similarly, Exhibit 2 is a Kolaskar analysis of SEQ ID NO:4 (PPIase), a 272-amino acid protein, which shows SEQ ID NO:4 contains even more antigenic regions than SEQ ID NO:2.

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[1] Kolaskar *et al.*, "A semi-empirical method for prediction of antigenic determinants on protein antigens." FEBS Lett. (1990) 276:172-4. A copy is enclosed with the accompanying Information Disclosure Statement.

It is highly unlikely that changing 3 in 10 amino acids in these proteins would destroy all epitopes and not result in new ones being formed. Indeed, the Office Action agrees that antibodies would be generated by proteins having 70% homology to SEQ ID NOS: 2 and 4: "microbial polypeptides having up to 30% non-identity with the native proteins are expected in the art to generally induce some antibodies." Office Action at page 5.

The Office Action cites two articles cited by the Office in support of its position. McGuinness 1993[2] is cited as teaching that amino acid changes are associated with "loss of subtype specificity" in a meningococcal protein. Office Action at page 6. McGuinness 1991[3] is cited as teaching that "a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the porA gene of a strain of Neisseria meningitidis of subtype P1.7, 16 resulted in 'striking changes in the structural and immunological properties of the class 1 protein' of this isolate." Office Action at page 6. But neither reference suggests that amino acid changes result in a protein that cannot induce an immune response. Rather, these papers show that one region of the protein has a mutated epitope such that a particular antibody has a partial or complete loss in binding to the epitope. Other antibodies can still bind to the protein, and other antibodies may now bind to the new epitope. Losing one epitope in a protein does not prevent the entire protein from being immunogenic.

[2] McGuinness *et al.*, "Class 1 outer membrane protein of *Neisseria meningitidis*: epitope analysis of the antigenic diversity between strains, implications for subtype definition and molecular epidemiology," Mol Microbiol. 1993 Feb;7(4):505-14.

[3] McGuinness *et al.*, "Point mutation in meningococcal *por A* gene associated with increased endemic disease," Lancet. 1991 Mar 2;337(8740):514-7.

Claims 1, 2, and 4 recite immunogenic compositions; *i.e.*, compositions that can raise an immune response in a mammal such as antibody production. See specification at page 8, lines 3-12. Each protein is several hundred amino acids long and would contain numerous antigenic regions. Indeed, as the Office Action acknowledges, the entire genus of proteins having 70% identity to the recited SEQ ID NOS would induce antibodies. In view of these facts, there is no scientific or legal support for rejecting claims 1, 2, and 4 as inadequately described. These arguments apply with equal or greater force to new claims 18-21.[4]

Please withdraw the rejection.

Rejection Under 35 U.S.C. § 112 ¶ 2

Claims 1, 2, and 4 stand rejected under 35 U.S.C. § 112 ¶ 2 as indefinite for use of the abbreviations PPIase and OmpA. Applicants have amended claim 1 to recite the full names with abbreviations within parentheses as the Patent Office suggests.

Claims 2 and 4 are rejected as indefinite for reciting proteins having 70% identity to SEQ ID NOS:2 and 4, respectively, in conjunction with a lower limit of at least 10 amino acids in size. Amended claims 2 and 4 do not recite the objected to language.

Claims 1, 2, and 4 are rejected as indefinite for improper antecedent basis. Claims 1, 2, and 4 are amended to provide proper antecedent basis.

Please withdraw the rejections.

[4] The rejection does not apply to new claim 22, which recites SEQ ID NO:2 and 4.

Rejection Under 35 U.S.C. § 102(b)

Claims 1, 2, and 4 stand rejected under 35 U.S.C. § 102 as anticipated by Carson.[5]

The Office Action contends that because the claims do not recite isolated and/or purified antigens, they read on whole cells of *Neisseria gonorrhoeae.* Office Action at page 10. Carson is also cited as teaching a "whole cell lysate of FA1090 strain of *Neisseria gonorrhoeae,*" and as teaching a "composition comprising proteins separated from said whole cell lysate." *Id.*

Amended claim 1 recites components that consist of substantially pure gonoccoal antigens, where substantially pure means that the proteins are "substantially free from other neisserial or host cell proteins." Specification at page 6, lines 31-32. The Office has the initial burden of providing facts and/or technical reasoning to support an inherent anticipation rejection. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). Here, the rejection provides no extrinsic evidence to support the assertion that Carson inherently discloses OmpA or PPIase in substantially pure form, and Applicants are not aware of any scientific facts which could provide such evidence.[6] It is well known that a one-dimensional polyacrylamide gel "fails to resolve complex protein mixtures satisfactorily, because of the masking effect due to the presence of proteins with similar charge and molecular weight."[7]

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[5] Carson *et al.*, "Ferric enterobactin binding and utilization by *Neisseria gonorrhoeae*," J Bacteriol. 1999 May;181(9):2895-901.

[6] If the Examiner is relying on personal information, Applicants request an affidavit under 37 C.F.R. § 1.104(d)(2) with the next Office Action.

[7] Basha, "Two-Dimensional Gel Electrophoretic Separation of Proteins," in Methods for Protein Analysis, Cherry & Barford, eds., American Oil Chemists' Society, Champaign, IL, page 70, 1988. A copy is enclosed with the accompanying Information Disclosure Statement.

The rejection includes no evidence that the polyacrylamide gels in Carson could separate OmpA and PPIase from proteins with close molecular weights. Most polyacrylamide gels are cast with an acrylamide-bisacrylamide molar ratio of 1:29,[8] and nothing in Carson suggests the gels were made using anything other than the typical 1:29 molar ratio. Gels made with a 1:29 molar ratio cannot resolve polypeptides that are less than 3% different in size. *Id.* Because the *Neisseria gonorrhoeae* FA1090 proteome contains many proteins less than 3% different in size from each of OmpA (Table 1)[9] and PPIase (Table 2), Carson cannot teach a substantially pure antigen as recited in claim 1.

Protein RefSeq No.	Molecular Weight (kDa)	% Difference from OmpA
OmpA	23.42	0
YP_207468.1	23.68	1.11
YP_208708.1	22.95	2.01
YP_207273.1	23.60	0.77
YP_208309.1	23.78	1.54
YP_207378.1	23.57	0.64
YP_208958.1	23.44	0.08
YP_208596.1	24.00	2.47
YP_208530.1	23.46	0.17
YP_208499.1	22.82	2.56
YP_208490.1	23.18	1.02

Table 1. Proteins less than 3% different in size than OmpA.

[8] Sambrook *et al.*, Molecular Cloning: a Laboratory Manual 2nd Edn, 1989. Vol 3, Page 18.48. A copy is enclosed with the accompanying information disclosure statement.

[9] Tables 1 and 2 were prepared from the information in Exhibits 3 and 4, respectively. Exhibits 3 and 4 contain copies of entries from an FA1090 proteome database. The listed proteins have a molecular weight within 3% of Omp A (23.42 kDa), Exhibit 3, and within 3% of PPIase (28.93 kDa), Exhibit 4. The proteome information is maintained in the FA1090 proteome database at http://www.expasy.org/sprot/hamap/NEIG1.html. The molecular weights for each protein are listed in the database and were calculated based on translation of coding sequences submitted to EMBL-Bank/Genbank/DDBJ databases.

Protein RefSeq No.	Molecular Weight (kDa)	% Difference from PPIase
PPIase	28.93	0
YP_208642.1	28.65	0.96
YP_208704.1	29.30	1.28
YP_207543.1	28.75	0.62
YP_208836.1	28.17	2.60
YP_208550.1	29.51	2.00
YP_208277.1	28.29	2.21
YP_208754.1	28.62	1.07
YP_208841.1	28.80	0.45
YP_207948.1	28.94	0.03

Table 2. Proteins less than 3% different in size than PPIase.

The rejection has not satisfied the elements of a *prima facie* case of inherent anticipation of a component consisting of the substantially pure antigen recited in claim 1 because there is no evidence of record that the Carson gel could separate PPIase and OmpA from other proteins of essentially the same molecular weight. Carson does not anticipate independent claim 1 or dependent claims 2 and 4. These arguments apply with equal force to new claims 18-22.

Please withdraw the rejection.

Rejection Under 35 U.S.C. § 102(a)

Claims 1, 2, and 4 stand rejected under 35 U.S.C. § 102 as anticipated by Fontana. Applicants respectfully traverse the rejection.

Fontana is cited as allegedly teaching a composition comprising gonoccoal antigens such as the OmpA amino acid sequence of SEQ ID NO:2 and the PPIase sequence of SEQ ID NO:4. Office Action at page 11.

To be anticipated, claimed subject matter must be disclosed "clearly and unequivocally" in the reference. *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A 1972) ("Thus,

for the instant [anticipation] rejection . . . to have been proper, the . . . reference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.").

Fontana discloses a multitude of sequences and provides no direction to select any particular combination. Fontana discloses proteins from *N. gonorrhoeae* listed in even-numbered SEQ IDs from 2 to 8622. See page 1, lines 16-18. In other words, Fontana provides a laundry list of 4311 proteins from which the Patent Office picks sequences corresponding to OmpA and PPIase. But such selection is not permitted. Here, as in *Arkley*, there is "nothing in the teachings relied upon by the Patent Office which 'clearly and unequivocally' directs those skilled in the art to make this selection." *Arkley*, 455 F.2d at 588. Applicants' disclosure clearly and unequivocally directs the artisan to Applicants' combination. However, the Patent Office may not use Applicants' guidance to arrive at the claimed subject matter.

The Patent Office is prohibited from picking and choosing sequences from those listed in the Fontana reference to arrive at the claimed subject matter.

Please withdraw the rejection.

Respectfully submitted,

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